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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 04/23/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/836,548

Applicant(s)
DREWE et al.

Examiner
Brenda Coleman

Art Unit
1624



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Feb 5, 2003
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14, 22-40, and 47-97 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14, 22-40, and 47-97 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9 6) ☐ Other:

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DETAILED ACTION

Claims 1-14, 22-40 and 47-97 are pending in the application.

This action is in response to applicants' amendment filed February 5, 2003. Claims 15-21 and 41-46 have been canceled, claims 1, 5, 6, 14, 22, 28, 36, 48-53, 56-61, 63, 66-70, 72, 73, 75-80, 82 and 86 have been amended and claims 94-97 are newly added.

Response to Amendment

Applicant's amendments filed February 5, 2003 have been fully considered with the following effect:

1. With regards to the rejection as being drawn to an improper Markush group of the last office action, the applicant's arguments have been fully considered but are not found persuasive. The applicant's stated that the "claims as amended refer only to compounds of the elected invention", however, this is not so.

In re Weber 198 USPQ 328 states that "[a] Markush-type claim is directed to "independent and distinct inventions," is two or more of its members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s)". Weber goes on to state in the next paragraph that "[i]f the claim is of that nature, the examiner is authorized to reject it as an improper Markush claim and for misjoinder under 35 U.S.C. 121 and to require the applicant to restrict the application to a single invention".

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A reference anticipating one invention, would not render obvious the others, for example a thiazepine ring is different from thiazocine, thiazine, thiazolidine, etc. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The elected invention which was examined in pending claims 1-14, 22-40 and 47-97, is drawn to compounds, compositions and method of use of the compounds of formula I where the ring A² forms a thiazepine ring. Claims 1-5, 35, 49, 51, 54-59, 62, 64, 66-68, 75-78 and 85-97 claim "A² is a monocyclic ring selected from heteroarylene or unsaturated, partially unsaturated or saturated heterocycloalkylene containing a total of 5 to 11 ring atoms" as well as species claimed in claims 62, 64, 71, 81, 83, etc.

Claims 1-5, 35, 49, 51, 54-59, 62, 64, 66-68, 75-78 and 85-97 are rejected as being drawn to an improper Markush grouping. For reasons of record and stated above.

2. With regards to the 35 U.S.C. § 112, first paragraph rejection of claims 1-14, 22-40, 47-50 and 52-93 of the last office action, applicants' stated that "prodrug" is a term of art, well known to one of ordinary skill in the art. However, the definition of prodrug in the specification is such that "prodrug means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of the invention".

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The term prodrug is of indeterminate scope in that they vary widely from drug to drug. It is not known which moiety of formula (I) would form the basis for the prodrug. Every ester, amide and carbamate in theory is biohydrolyzable, i.e. is capable in some degree of hydrolyses. Not to mention the many in vivo environments that this occurs in.

It is the Wands factors which are used to evaluate the enablement question. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the invention in the instant case, has claims which embrace substituted thiazepine compounds. The instant compounds of formula (I) wherein the prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by claims 1-14, 22-40 and 47-97. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

Claims 1-14, 22-40 and 47-97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

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one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. For reasons of record and stated above.

3. With regards to the 35 U.S.C. § 112, first paragraph rejection of claims 54-56 and 66-88 in the last office action, the applicants' arguments have been fully considered, however they were not found persuasive. In the art of clinical oncology, no compound has yet shown clinical efficacy against every type of cancer. To quote Salmon (Principles of Cancer Therapy) in the paragraph on page 1038 titled Medical Therapy "Curative therapy has been developed for a series of relatively uncommon neoplasms and useful palliative therapy has been developed for some common forms of cancer (Table 162-4). With rare exceptions, effective therapy has utilized combinations of anticancer drugs." Applicant's attention is drawn to Tables 162-6, 162-7, 162-8, 162-162-9, 162-10, and the material on pages 1045-1046 titled Miscellaneous Anticancer Agents in Salmon (Principles of Cancer Therapy). Different agents are used for different specific forms of cancer and no single agent is listed as a treatment of every single type of cancer. To quote Balasubramanian (Recent Developments in Cancer Cytotoxics) from page 151 first paragraph "[t]he successful treatment of solid tumors remains a formidable challenge. The partial success of traditional cancer chemotherapy...". On page 158, second paragraph Balasubramanian (Recent Developments in Cancer Cytotoxics) states: "The future scenario in clinical management of cancer will be mainly dictated by the availability of less toxic and tumor selective agents". No compound has shown clinical efficacy against all cancers, thus no *in vivo* or *in vitro* assay could be validated

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for the identification of such a general agent. Applicants' specification logically must lack such assay data.

To make clearer the lack of enablement for treatment of all cancer, extrinsic evidence is supplied by Draetta (Ann. Reports Med. Chem.), final sentence on page 246 "Although many still think about the need for a magic bullet as a cure for all cancers, our knowledge of the molecular mechanism underlying this disease make the prospect of developing such a universal cure very unlikely." Since no universal cure for cancer has been developed, it follows that there is no correlation between the assays relied upon by applicants and the ability to treat all cancers. Thus, those assays are not sufficient to enable such claims.

Claims 54-88 and 95-97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. For reasons of record and stated above.

4. The applicant's amendments and arguments are sufficient to overcome the 35 USC § 112, first paragraph rejection of claims 55, 56, 85 and 86, labeled paragraph 7 in the last office action, which is hereby withdrawn.

5. With regards to the 35 USC § 112, first paragraph rejection of claims 57-65 and 89-93 in the last office action, the applicants' arguments have been fully considered but are not found persuasive. The applicants' stated that "it is well known to those of skill in the art what disorders

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are responsive to the induction of apoptosis” and O’Reilly and Orrenius are cited in support. However, O’Reilly and Orrenius are not of record in the file. The applicants indicated that an Information Disclosure Statement was filed November 4, 2002, however, there is no IDS of record filed on November 4, 2002.

There is no basis for the treatment of the asserted diseases and/or disorders in the specification, nor is there any testing to indicate that the compounds of the instant invention are effective in the treatment of the asserted diseases and/or disorders.

Claims 57-65, 89-93, 96 and 97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. For reasons of record and stated above.

6. The applicant’s amendments and arguments are sufficient to overcome the 35 U.S.C. § 112, second paragraph rejections labeled a), b), c), d), f), g), h), i), j), k), l), m), n), o), p), q), r), s), t), u), v), w), x), y), z), aa), ab), ac), ad), ae), af), ah) and ai) of the last office action, which are hereby **withdrawn**. However, with regards to the 35 U.S.C. § 112, second paragraph rejection labeled e) and ag) the applicant’s amendments and remarks have been fully considered but they are not persuasive.

- e) The applicants’ stated that “it is a derivative of a compound of Formula I in which the nitrogens are in an oxidized state and which possess the desired pharmacological activity” and it is a derivative of a compound of Formula I in

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which a reactive site or sites are blocked with protecting groups". Derivatives includes more than is positively recited. With respect to derivatives, the applicant's specification does not sufficiently define the applicants metes and bounds of the compounds as claimed herein. It is recognized that a protecting group is often used in a process, however, it is the compounds which are being claimed and "protected derivatives" does not define the compounds which the applicants are seeking patent protection for.

- ag) The applicants' stated that "the test for indefiniteness is whether one skilled in the art would understand the bounds of the claims when read in light of the specification". For example claim 57 generically claims the method of treating a disorder responsive to the induction of apoptosis. The rejection of claims 57-65 , 89-93, 96 and 97 was on the grounds that they are indefinite, in that it is not known which diseases are capable of being responsive to the induction of apoptosis. The scope of diseases and/or disorders associated with the induction of apoptosis could alter over time. The applicants' are not entitled to preempt the efforts of others.

Claims 1-14, 22-40 and 47-97 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For reasons of record and stated above.

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7. The applicant's amendments and arguments are sufficient to overcome the 35 U.S.C. § 102, anticipation rejection of the last office action, which is hereby **withdrawn**.

In view of the amendment dated February 5, 2003, the following new grounds of rejection and/or reinstated rejections apply:

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 97 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The addition of claim 97, which includes a list of disorders, some which are not described in the specification, i.e. rheumatoid arthritis, autoimmune lymphoproliferative syndrome, etc.

Applicant is required to cancel the new matter in the reply to this Office action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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9. Claims 1-5, 8, 22, 24, 26, 35, 48, 49, 51-64, 66-72, 75-83 and 85-97 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

- a) Claims 1-5, 22, 24, 26, 35, 49, 51, 54-59, 66-68, 75-78 and 87-97 are vague and indefinite in that it is not known what is meant by the definition of R^1 , where R^1 is as defined below. There is no definition of R^1 below.
- b) Claims 1-5, 35, 49, 51, 54-59, 62, 64, 66-68, 75-78 and 85-97 recite the limitation " A^2 is a **fused polycyclic ring system**" in the proviso. There is insufficient antecedent basis for this limitation in the claim.
- c) Claims 8, 63, 72 and 82 recite the limitation "bis-trifluoromethyl-phenyl" in the species on pages 102, 132, 145 and 158, respectively. There is insufficient antecedent basis for this limitation in the claim.
- d) Claim 48 is vague and indefinite in that it is not known what is meant by the definition of A^2 , where A^2 is as defined above. There is no definition of A^2 above.
- e) Claims 51-53 are vague and indefinite in that it is not known what is meant by the definition of A^2 is $-R^8$. It is believed that the applicants' intended $-X^2R^8$.
- f) Claims 51-53 are vague and indefinite in that it is not known what is meant by the definition of A^3 is $-R^9$. It is believed that the applicants' intended $-X^2R^9$.
- g) Claims 57-59 are vague and indefinite in that it is not known what is meant by the definition of A^1 is $-R^3$. It is believed that the applicants' intended $-X^2R^3$.

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- h) Claims 57-61 are vague and indefinite in that it is not known what is meant by the definition of A^2 is $-R^8$. It is believed that the applicants' intended $-X^2R^8$.
- i) Claims 57-61 are vague and indefinite in that it is not known what is meant by the definition of A^3 is $-R^9$. It is believed that the applicants' intended $-X^2R^9$.
- j) Claim 62 recites the limitation "benzo[b][1,4]thiazepin-4-yl" in the three of the species. There is insufficient antecedent basis for this limitation in the claim.
- k) Claim 64 recites the limitation "benzo[b][1,4]thiazepin-4-yl" in the two of the species. There is insufficient antecedent basis for this limitation in the claim.
- l) Claims 66-68 are vague and indefinite in that it is not known what is meant by the definition of A^1 is $-R^3$. It is believed that the applicants' intended $-X^2R^3$.
- m) Claims 66-70 are vague and indefinite in that it is not known what is meant by the definition of A^2 is $-R^8$. It is believed that the applicants' intended $-X^2R^8$.
- n) Claims 66-70 are vague and indefinite in that it is not known what is meant by the definition of A^3 is $-R^9$. It is believed that the applicants' intended $-X^2R^9$.
- o) Claim 71 recites the limitation "benzo[b][1,4]thiazepin-4-yl" in the three of the species. There is insufficient antecedent basis for this limitation in the claim.
- p) Claims 76-78 are vague and indefinite in that it is not known what is meant by the definition of A^1 is $-R^3$. It is believed that the applicants' intended $-X^2R^3$.
- q) Claims 76-78 are vague and indefinite in that it is not known what is meant by the definition of A^2 is $-R^8$. It is believed that the applicants' intended $-X^2R^8$.

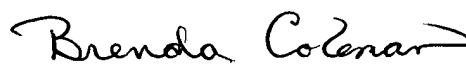
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- r) Claims 76-80 are vague and indefinite in that it is not known what is meant by the definition of A^3 is $-R^9$. It is believed that the applicants' intended $-X^2R^9$.
- s) Claim 81 recites the limitation "benzo[b][1,4]thiazepin-4-yl" in the three of the species. There is insufficient antecedent basis for this limitation in the claim.
- t) Claim 83 recites the limitation "benzo[b][1,4]thiazepin-4-yl" in one of the species. There is insufficient antecedent basis for this limitation in the claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner can normally be reached on Mondays from 8:30 AM to 5:00 PM, on Tuesdays from 8:00 AM to 4:30 PM, on Wednesday thru Friday from 9:00 AM to 5:30 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.



Brenda Coleman
Primary Examiner AU 1624
April 21, 2003